



NDA 21-548

GlaxoSmithKline
Attention: Anne Stokely, M.S.P.H.
Director, Antiviral/Anti-infective Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Stokely:

Please refer to your new drug application (NDA) dated December 19, 2002, received December 20, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LEXIVA™ (fosamprenavir calcium) 700 mg Tablets.

We acknowledge receipt of your submission(s) dated January 15, 2003, January 24, 2003, February 19, 2003, February 24, 2003, March 6, 2003, March 11, 2003, March 21, 2003, April 2, 2003, April 16, 2003, April 18, 2003, April 29, 2003, May 15, 2003, May 21, 2003, May 28, 2003, June 11, 2003, July 9, 2003, July 17, 2003, July 18, 2003, July 24, 2003, July 31, 2003, August 1, 2003, August 8, 2003, August 11, 2003, August 13, 2003, August 20, 2003, August 21, 2003, September 3, 2003, September 4, 2003, September 12, 2003, September 18, 2003, September 24, 2003, September 25, 2003, September 29, 2003, October 3, 2003, October 9, 2003, October 10, 2003, October 13, 2003, October 17, 2003, and October 20, 2003.

This new drug application provides for the use of LEXIVA™ (fosamprenavir calcium) 700 mg Tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, this application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels) and/or submitted labeling (package insert submitted October 20, 2003, patient package insert submitted October 20, 2003, immediate container and carton labels submitted October 16, 2003). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and (an) unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-548.**" Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated October 17, 2003. These commitments are listed below.

1. Submit the results of *in vitro* testing for combination activity relationships with efavirenz and delavirdine, using conventional methodology.

Study start – Ongoing.

Final report submission – within 6 months of the date of this letter.

2. Provide data on the anti-HIV activity *in vitro* of amprenavir against multiple isolates from each of the HIV-1 clades and multiple isolates of HIV-2, using conventional methodology.

Study start – Ongoing.

Final report submission – within 6 months of the date of this letter.

3. Complete ongoing carcinogenicity studies in mice and rats and submit final reports.

Protocol submissions – Completed.

Study start – Ongoing.

Final reports submission – within 33 months of the date of this letter.

4. Conduct 90-day rat toxicity studies on the (b)(4)----- associated with the manufacture of fosamprenavir calcium.

Submission of study design for comment – within 2 months of the date of this letter.

Study start – within 4 months after receiving feedback from DAVDP on the proposed study design.

Final report submission – within 18 months after study initiation.

5. Conduct human drug-drug interaction study of fosamprenavir calcium twice daily and nevirapine and fosamprenavir calcium/ritonavir twice daily and nevirapine.

Protocol submission – Completed.

Study start – Ongoing.

Final report submission – within 14 months of the date of this letter.

6. Conduct a human drug-drug interaction study of fosamprenavir calcium twice daily and a proton pump inhibitor, and fosamprenavir calcium/ritonavir twice daily and a proton pump inhibitor.

Submission of study design for comment – within 3 months of the date of this letter.

Study start – within 4 months after receiving feedback from DAVDP on the proposed study design.

Final report submission – within 12 months after study initiation.

7. Conduct a pharmacokinetic study with fosamprenavir calcium/ritonavir in patients with hepatic impairment to determine dosing.

Submission of study design for comment – within 3 months of the date of this letter.

Study start – within 4 months after receiving feedback from DAVDP on the proposed study design.

Final report submission – within 18 months after study initiation.

8. Conduct a human drug-drug interaction study of fosamprenavir calcium/ritonavir twice daily with atazanavir.

Submission of study design for comment – within 4 months of the date of this letter.

Study start – within 6 months after receiving feedback from DAVDP on the proposed study design.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **“Postmarketing Study Protocol”, “Postmarketing Study Final Report”, or “Postmarketing Study Correspondence.”**

Furthermore, please note that although the FDA recognizes the following intentions are not postmarketing study commitments, the completion and submission of these agreements are highly encouraged:

- Continue to evaluate the underlying mechanism of the interaction between fosamprenavir and lopinavir/ritonavir.
- Continue to evaluate amprenavir’s role as a CYP3A4 inhibitor.

We remind you that you must submit patent information on form FDA 3542, *Patent Information Submitted Upon and After Approval of an NDA or Supplement*, within 30 days of the date of this letter as required by 21 CFR 314.53(c)(2)(ii) and 314.53(d)(2) at the address provided by 21 CFR 314.53(d)(4). The form may be obtained at:

<http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>. To expedite review of this patent declaration form, we request you submit an additional copy of the form to this application and to the Center for Drug Evaluation and Research "Orange Book" staff at

Food and Drug Administration
Office of Generic Drugs, HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the

court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Antiviral Drug Products (DAVDP) and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Destry Sullivan, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Debra Birnkrant
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